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Model-based lamotrigine clearance changes during pregnancy: clinical implication

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Abstract

Objective: The objective of the study was to characterize changes in the oral clearance (CL/F) of lamotrigine (LTG) over the course of pregnancy and the postpartum period through a model-based approach incorporating clinical characteristics that may influence CL/F, in support of developing clinical management guidelines. **Methods**: Women receiving LTG therapy who were pregnant or planning pregnancy were enrolled. Maternal blood samples were collected at each visit. A pharmacokinetic analysis was performed using a population-based, nonlinear, mixed-effects model. **Results**: A total of 600 LTG concentrations from 60 women (64 pregnancies) were included. The baseline LTG CL/F was 2.16 L/h with a between-subject variability of 40.6%. The influence of pregnancy on CL/F was described by gestational week. Two subpopulations of women emerged based on the rate of increase in LTG CL/F during pregnancy. The gestational age-associated increase in CL/F displayed a 10-fold higher rate in 77% of the women (0.118 L/h per week) compared to 23% (0.0115 L/h per week). The between-subject variability in these slopes was 43.0%. The increased CL/F at delivery declined to baseline values with a half-life of 0.55 weeks. **Interpretation**: The majority of women had a substantial increase in CL/F from 2.16 to 6.88 L/h by the end of pregnancy, whereas 23% of women had a minimal increase. An increase in CL/F may correspond to decreases in LTG blood concentrations necessitating the need for more frequent dosage adjustments and closer monitoring in some pregnant women with epilepsy. Postpartum doses should be tapered to preconception dose ranges within 3 weeks of delivery.

Introduction

Epilepsy and bipolar disorder are common conditions that often require continuous treatment with antiepileptic drugs (AEDs) during pregnancy to protect the mother and the developing fetus from the harmful effects of uncontrolled disease. Lamotrigine (LTG) is a clinically viable option to treat epilepsy and bipolar disorder in pregnant women[1,2] in large part due to low relative risks of teratogenic complications and adverse neurodevelopmental effects compared to other medication options.[3–8] However, LTG pharmacokinetics markedly change during pregnancy[9–18] and if a woman with epilepsy remains on her pre-pregnancy LTG dose, concentrations may decrease significantly and lead to an increase in seizure frequency for some women.[10,13,19] The clinical impact of declining LTG concentrations during pregnancy in women with bipolar disorder is less clear. The American Academy of Neurology Guidelines states that monitoring of LTG levels during pregnancy

should be considered (Level B), but these guidelines fall short of providing specific recommendations regarding frequency and/or gestational timing of monitoring. This is complicated further by the marked individual variability seen in LTG clearance across pregnancy.[10,15] More systematic information is needed regarding LTG pharmacokinetic alterations during pregnancy and postpartum to direct clinical care during these vulnerable life stages.[20] In the United States, many neurologists monitor LTG blood levels frequently when treating women with epilepsy during pregnancy, but practices vary between once per trimester to once per week. Conversely, perinatal monitoring of LTG concentrations has not emerged as a common practice among psychiatrists treating women with bipolar disorder.

LTG is moderately protein bound (55%) and has a relatively long half-life (23–37 h).[21–25] It is mainly metabolized in the liver by UDP-glucuronosyltransferases (UGT) 1A4.[26–28] UGT1A4 is also present in the placenta at term.[29] Previous studies demonstrate that LTG oral clearance (CL/F) increases up to 250% during pregnancy[9–11,15,16] and rapidly declines to preconception values within 2–4 weeks post-delivery.[9,10,14–17] Estrogens but not progestins reduce LTG serum levels in women receiving oral hormonal contraceptives.[30] The rising levels of estrogens during pregnancy may induce the UGT enzyme system[31] and consequently increase the metabolism of LTG leading to decreases in LTG concentrations.

Several studies demonstrate changes in LTG CL/F during gestation,[9–18] with one systematic analysis with 14 women showing that perinatal week is a predictor of CL/F.[15] The objective of this study was to build a model to describe the LTG CL/F time course changes during and after pregnancy in a larger group of pregnant women who are taking LTG as part of their usual clinical therapy. This approach allowed us to evaluate the changes in CL/F throughout pregnancy and to quantify between-subject variability in the parameters that describe the change in time course.

Methods

Study population

The study was approved by the Institutional Review Board of Emory University School of Medicine. Subjects included in this analysis were women ≥17 years of age treated with LTG for epilepsy and/or a psychiatric disorder, most commonly bipolar. Patients received LTG for the clinical indication of epilepsy, a psychiatric disorder, or both. For this study, exclusion criteria included significant medical issues (uncontrolled thyroid disease, severe anemia, kidney or liver dysfunction or progressive cerebral disease), use of alcohol or recreational drugs, history of medication nonadherence, inability to keep daily seizure diaries personally or with the help of a caregiver if the woman had epilepsy, and active suicidal ideation. Written informed consent was obtained from each woman before enrollment. Some subjects used in this population-based pharmacokinetic analysis have been included in a previous analysis.[10]

Study design

Pregnant women or those planning a pregnancy were enrolled in a prospective observational study to investigate pharmacokinetic changes in neurotropic agents including AEDs during pregnancy (Emory Women's Epilepsy and Women's Mental Health Programs). All women in the epilepsy cohort recorded use of all medications and missed LTG doses in a daily diary; women with epilepsy combined this with daily seizure diaries. Patients were followed every 1–3 months during pregnancy and the first postpartum year. For women with epilepsy, a neurologic examination and review of subject diary were completed at each visit. In women with bipolar disorder, a structured clinical interview for DSM-IV diagnosis was completed in conjunction with serial administration of symptom rating scales at visits scheduled every 4–6 weeks. In addition, intervening illnesses and obstetrical complications, if any, were recorded for all participants. At each visit, body weight (WT), body mass index (BMI), and gestational age (GA) in weeks or postpartum weeks (PPW) were recorded. Maternal blood was collected at each study visit and occasionally at obstetric offices. Thus, the LTG concentrations were not necessarily trough levels. Hours post dose were recorded. For epilepsy patients, doses were adjusted for each subject depending on her clinical status and comparison of the clinically obtained LTG concentrations to the individual's baseline target concentration. For patients with bipolar disorder, doses were adjusted at the discretion of the treating psychiatrist in response to evolving presentation of symptoms.

LTG concentration analysis

Blood was centrifuged at 1691 *g*, 3°C for 10 min, and 600 μL aliquots of plasma/serum were transferred to polypropylene tubes. The plasma/serum samples were frozen at −80°C until analysis. Total LTG concentrations were measured using a validated assay employing high performance liquid chromatography with ultraviolet detection (Chromsystems, GmbH, Munich, Germany).[32] The lower and upper limit of quantification of the bioanalytical assay was 0.25 and 20 μg/mL, respectively. Both

the intra-assay and interassay coefficient of variations (CVs) were <12.5%.

Pharmacokinetic analysis

The pharmacokinetic analysis was performed using a population-based, nonlinear, mixed-effects model (NONMEM version 7; ICON Development Solutions, Ellicott City, MD). LTG exhibits first-order linear pharmacokinetics that can be well described by a one compartmental model.[33] Due to the relatively long time period between pregnancies, women who had a second pregnancy were treated as independent subjects. We chose to model all observations as being steady state concentrations. This decision was based on two important characteristics of this dataset. First, LTG elimination half-life (23–37 h) is relatively long compared to dosing intervals in the majority of the patients. This results in minimal changes in concentrations in the course of a day. Also, as volume of distribution is suspected to increase over the course of pregnancy we would need to have data to estimate the parameter. This dataset did not include information that allowed estimation of volume of distribution. Blood samples were obtained at least 7 days after any change in maternal daily dose and steady state conditions were assumed. As observed concentrations could be assumed to be at steady state and fluctuating little over the dosing interval, they could be reasonably predicted using a steady state infusion model (eq. 1).

$$C_{obs} = \frac{\text{DoseRate}}{\text{CL/F}} \quad (1)$$

where the Dose Rate is the LTG total daily dose divided by 24 h and CL/F is the apparent clearance of LTG.

Primary modeling efforts were focused on characterizing the time course of changes in LTG CL/F before pregnancy, during pregnancy, and after delivery. Intuitively, our model needed to capture a pre-pregnancy CL/F, some functional form that allowed CL/F to increase during pregnancy with a relatively rapid decrease following delivery, and a stable postpartum CL/F. The characteristics of this model can be seen in Figure 1. In addition, our modeling approach tested the effect of subject characteristics of maternal and GA, body size, indication (epilepsy or no epilepsy), and race on LTG CL/F (χ^2,

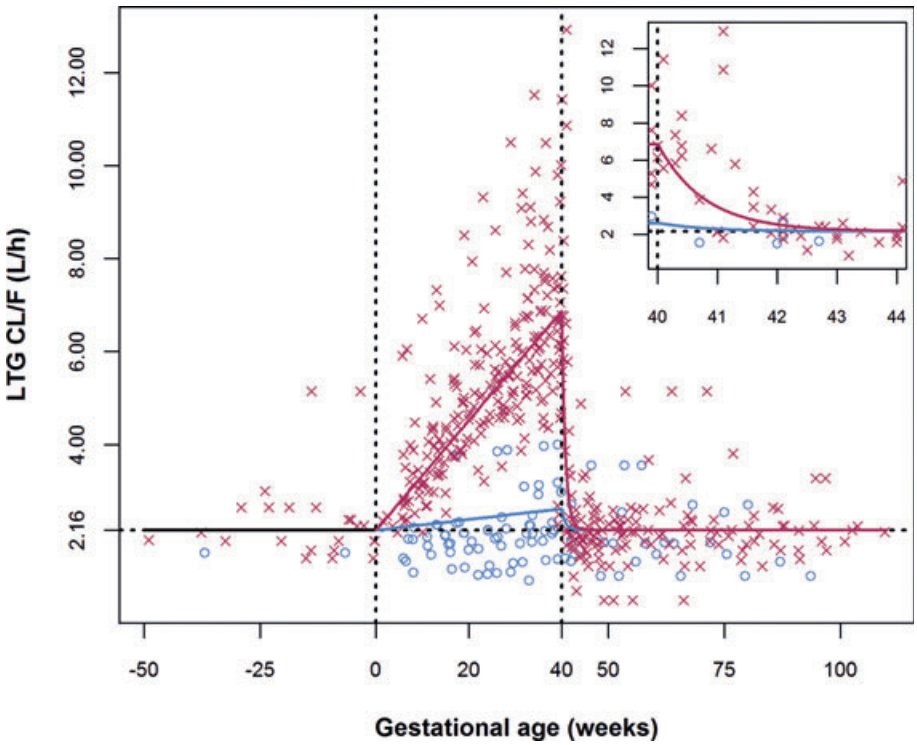

Figure 1. Individual estimates (post hoc estimates) of LTG CL/F during different stages of pregnancy. Maroon and blue data points indicate the post hoc CL/F estimates for subjects with higher rate of increase (population I) and lower rate of increase (population II) in CL/F during pregnancy, respectively. Solid lines through the data indicate population predicted CL/F profiles. Vertical dashed lines at gestational age 0 and 40 weeks separate stages of pregnancy (<0 weeks: preconception; 0–40 weeks: pregnant; >40 weeks: postpartum). Inset plot displaying the data and population model predictions of first four postpartum weeks. Horizontal dashed line in the plot represents baseline CL/F (2.16 L/h).

$\alpha = 0.05$, df = 1). The final pharmacokinetic model was evaluated for precision and internal predictive ability using a bootstrap procedure and standardized visual predictive checks, respectively. For a detailed description of the NONMEM modeling methodology, see the data supplement for this article.

Results

Study population

Sixty women (64 pregnancies) met the inclusion criteria providing 600 total LTG concentrations over the perinatal period. Forty-three pregnancies were in women diagnosed with epilepsy, 19 pregnancies in women with a psychiatric illness, and two pregnancies in patients with a comorbidity of epilepsy and a psychiatric illness. Baseline characteristics of the subjects are presented in Table 1. Distribution of the time of observations during the course of the study is presented in Table 2. Women were treated with LTG daily doses (50–1400 mg) over the course of the perinatal period. The majority of subjects were prescribed a twice-a-day dosing schedule (73%). Four observations were excluded from the analysis because of missing dose information.

Table 1. Summary of subject demographics.

Baseline characteristics	Mean ± SD or number
Number of subjects	60
Epilepsy	42
Non epilepsy	18
Number of pregnancies	64
Epilepsy	43
Non-epilepsy	21
Age (in years)	31.1 ± 5.5
Body weight (in kgs)	64.3 ± 12.7
Height (in meters)	1.65 ± 0.06
BMI (in kg/m^2)	23.9 ± 4.9
Race	
Whites	44
Blacks	10
Asians	4
Native Americans	2
Ethnicity	
Non-Hispanics	57
Hispanics	3

BMI, body mass index.

Pharmacokinetic analysis

The final model equations of LTG CL/F during pregnancy and postpartum are presented in Table 3. The simultaneous fitting of these model equations resulted in physiologically meaningful parameter estimates with considerable precision (Table 4). The baseline CL/F (CL_{BL}) was 2.16 L/h with a between-subject variability of 40.6%. The stable postpartum CL/F was found to be no different from the preconception value.

During pregnancy, the change in CL/F with GA was best described by a linear function with a slope parameter. Visual inspection of the plots of individual estimates of CL/F versus GA revealed two different groups of women each with a distinct rate of increase (slope) in CL/F (Fig. 1). With the exception of GA and PPW, we were not able to identify a covariate associated with these two groups of women. Therefore, we modified our model of the slope parameter to include two slopes using a mixture model. In a mixture model, one proposes the population is composed of subpopulations (two in our case) without a priori defining subjects to be in one population or the other. The NONMEM software assigns each subject to each population to determine which subpopulation is more likely given their data. The result is an estimate of the slope parameter for each group and an estimate of the fraction of subjects in each subpopulation. The mixture model indicated that a majority of women (77%) had a steeper slope of 0.118 L/h per week of GA, whereas 23% of pregnant women displayed a significantly flatter slope of 0.0115 L/h per week for each week of gestation. Any woman who had data from two pregnancies fell into the same group both times. This mixture model accounted for 76% of the between-subject variability in the slopes with a remaining between-subject variability of 43%.

Following delivery, a first-order monoexponential decline in CL/F as a function of PPW described the return of CL/F to baseline in the postpartum period with

Table 2. Distribution of samples and time dependent changes in covariates (mean ± SD) across the perinatal period.

Characteristic	PC (GA < week 0)	TM1 (0 < GA ≤ 14 weeks)	TM2 (14 < GA ≤ 28 weeks)	TM3 (28 weeks < GA < delivery)	PP (delivery to postpartum 70 weeks)
Subjects/pregnancies (*n*)	13	36	45	54	51
Maternal blood samples (*n*)	35	88	139	161	177
Body weight (in kgs)	68.9 ± 14.4	66.1 ± 11.6	71.5 ± 14.4	75.5 ± 13.2	69.9 ± 15.4
BMI (in kg/m^2)	26.0 ± 5.0	24.5 ± 4.5	27.1 ± 6.0	28.1 ± 5.0	25.8 ± 5.7

PC, preconception; TM, trimester; PP, postpartum; GA, gestational age; BMI, body mass index.

Table 3. Final model equations.

Stage	Model equation	Description
Preconception	$CL/F = CL_{BL}$	CL_{BL}: baseline CL/F
Pregnant	Population I: $CL/F = CL_{BL} + Slope_1 \times GA$	GA: gestational age
	Population II: $CL/F = CL_{BL} + Slope_2 \times GA$	Slope: rate of change in CL/F
Postpartum	$CL/F = \Delta CL_{DEL} \times \exp(-k \times PPW) + CL_{BL}$	ΔCL_{DEL}: CL/F change from baseline to delivery; *k*: first-order rate constant; PPW: postpartum weeks

Table 4. Final model parameter estimates.

Stage of pregnancy	Parameter	Estimate (% RSE)	Bootstrap median [2.5th, 97.5th percentile]
Preconception	CL_{BL} (L/h)	2.16 (6.4)	2.14 [1.90, 2.47]
	BSV in CL_{BL} (% CV)	40.6	39.6
Pregnant	$Slope_1$ (L/h per week)	0.118 (11.4)	0.117 [0.067, 0.155]
	$Slope_2$ (L/h per week)	0.0115 (53.0)	0.0115 [0.0012, 0.0872]
	Mixing fraction (population II)	0.23 (34.1)	0.25 [0.09, 0.617]
	BSV in slope (% CV)	43.0	40.0
Postpartum	*k* (1/week)	1.27 (10.5)	1.29 [1.09, 4.54]
	RUV (% CV)	45.7	45.5

CL_{BL}, baseline clearance; BSV, between-subject variability; RUV, residual unexplained variability; % CV, percent coefficient of variation; % RSE, percent relative standard error.

a half-life (0.693/*k*, the estimated first-order rate constant) of 0.55 weeks.

After taking into account the effects of both GA and PPW and allowing two slopes with the mixture model, the remaining unexplained variability was 45.7%. Maternal body size, maternal age, indication (epilepsy or no epilepsy), and race had no effect on any portion of our model (χ^2, $P > 0.05$, df = 1). The simulation-based model evaluation confirmed the internal predictive performance of the final model (see supplement for more detail).

Discussion

We characterized the changes in LTG oral CL before and during the course of pregnancy and in PPW with a nonlinear mixed-effects approach. A unique finding of our model-based analysis is the identification of two populations of women with different rates of increase in CL/F.

Overall, data were adequately characterized by a linear increase in LTG CL/F during pregnancy and a nonlinear exponential decline in CL/F after delivery. The population mean baseline CL/F (CL_{BL}) of 2.16 L/h is in close agreement with those reported (1.96–2.64 L/h) from other studies.[21–25,34–38] Furthermore, the magnitude of the between-subject variability in both the baseline CL/F (40.6%) and increased rates of oral CL (43.0%) during pregnancy are consistent with previous reports that noted a substantial interindividual variability in CL/F rates during pregnancy.[10,15,39]

Interestingly, while most women demonstrate a substantial increase in LTG CL/F during pregnancy, we identified a subpopulation of pregnant women that exhibited a very modest increase (Fig. 1). The main population included a majority of the pregnant women (77%) and displayed a 10-fold increase in LTG CL/F per week compared to the subpopulation. The estimated rate of increase in LTG CL/F for the main population (0.118 L/h per week) predicts 76%, 153%, and 219% increases of CL/F from baseline, while that of population II (0.0115 L/h per week) confers lower degrees of increase in LTG oral CL (7.5%, 15%, and 21%) by the end of the conventional first (14 weeks), second (28 weeks), and third (40 weeks) trimesters, respectively. Our estimated changes in LTG CL/F during pregnancy are in general agreement with previous studies of pregnant women that reported increases of 65–197%, 93–236%, and 88–250% in baseline LTG CL/F for the first, second and third trimesters, respectively.[9–11,15,16] Genotypic variations in the activity or induction of UGT1A4 could partly explain the varying degrees of enhanced oral CL between the two populations and may warrant further investigations.[16,40–42]

These findings are of clinical importance as they indicate that varying degrees of change in LTG CL/F are expected during gestation with some patients displaying a dramatic increase in their oral CL compared to others.

Therefore, we anticipate that the population of pregnant women with the larger increase in CL/F may require more frequent and higher dosage adjustments in order to maintain pre-pregnancy baseline levels. This group may also display greater variability in LTG concentrations during pregnancy than those in the smaller subpopulation of women exhibiting a minimal increase in LTG oral CL over the weeks of gestation.

In the PPW, the LTG CL/F declined in an exponential manner with a common estimated first-order rate constant (k) of 1.27 per week for both subpopulations. The calculated half-life ($0.693/k$) of the return to baseline CL/F was 0.55 weeks, indicating that LTG oral CL is expected to reach the baseline value within 3 weeks after delivery. This is consistent with the previous report from this study group stating that an empiric postpartum taper over the first 10 days to the preconception dose or preconception dose plus 50 mg prevents postpartum toxicity symptoms; in some women, preconception dose plus 50 mg was chosen to counteract the seizure-provoking effects of the inevitable sleep-disruption.[10] In addition, several previous studies determined a postpartum period of 2–4 weeks for LTG CL/F to reach preconception values in pregnant women receiving LTG.[9,10,14–17]

After accounting for GA and PPW, weight, race, clinical diagnosis/indication, and age were found to have no effect on LTG oral CL. Similarly, in a study of pregnant women maintained on LTG monotherapy Pennell et al.[15] found the changes of LTG oral CL during pregnancy and childbirth to be independent of WT. This is consistent with clinical observation in epilepsy patients that dose changes are needed in the first trimester even though there are small to no weight changes at this time in the pregnancy. Regarding age, our results remain consistent with the Pennell et al.[10] study who found the age of pregnant women to have no significant effect on LTG oral CL. The population of our study consisted of women of child-bearing age; therefore, by nature this population reflects a narrow age range (17–42 years) and may explain the lack of an age effect on LTG CL/F.

The satisfactory performance of the oral CL model may justify its applicability in dosing pregnant women on LTG monotherapy and those on LTG with no interacting medications. Once a patient's pattern of induction of clearance is determined during the first trimester or in a previous pregnancy, it may be possible to adjust the schedule for blood draws. For instance, if LTG concentrations drop by approximately 50% at the end of the first trimester it is likely the women will continue to exhibit increasing clearances throughout pregnant. The majority of women in the main subpopulation will likely require therapeutic drug monitoring at least once per month until delivery, while it may be possible to reduce the frequency of blood sampling to every 2–3 months in a smaller subpopulation of women. It may even be possible to make empiric dosage adjustments in this group if they have barriers to frequent blood draws such as cost or transportation. Further prospective studies that test the utility of this equation are needed.

In conclusion, we characterized the changes of LTG CL/F during the course of pregnancy and after delivery using a model-based approach. The major results of this analysis showed that LTG CL/F was significantly influenced by GA and PPW and identified the presence of two subpopulations of women with different rates of increases in CL/F during pregnancy. The rate of LTG clearance differed by 10-fold between groups with an estimated mixing fraction of 23% in the subpopulation meaning that during pregnancy, LTG CL/F increases from 2.16 L/h to 6.88 L/h in 77% of women, while in the remaining 23%, CL/F increases from the 2.16 L/h to only 2.62 L/h. This 219% increase in CL/F in the majority of women translates to a possible need for a substantial increase in daily LTG dose over the course of pregnancy to maintain a woman with an epilepsy patient's individual target concentration to avoid seizure worsening, and will almost certainly require close monitoring of concentrations. In the smaller group, the 21.3% increase in CL/F may not even necessitate an increase in dose. Unfortunately, no covariates could be identified to indicate which group any individual woman belonged. Further studies incorporating genotyping information and possibility of polymorphisms involved in the regulation and expression of UGT1A4 or induction-related estrogen receptors could be useful to identify the determinant of variation in LTG CL/F during pregnancy. Following childbirth, CL/F rapidly reached preconception values within 3 weeks. Thus, LTG doses should be tapered to preconception doses or slightly above within 3 weeks of delivery. Characterization of the factors influencing LTG CL/F will be valuable in optimizing the clinical management of women on LTG across the perinatal period. In addition, these factors may also be important considerations for management of other medications across the perinatal period.

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Conflict of Interest

Dr. Newport reports grants and personal fees from Eli Lilly, grants and personal fees from GlaxoSmithKline, grants from Janssen, grants and personal fees from Wyeth, personal fees from Pfizer, other from Astra-Zeneca, outside the submitted work. The other coauthors have no potential conflicts of interest to report.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Details of pharmacokinetic modeling and evaluation.

Figure S1. Observed versus population predicted (PRED) and observed versus individual predicted (IPRED) LTG concentrations, by stage of pregnancy (PC, preconception; PP, postpartum). Data points indicate the observed versus predicted plasma concentrations. Solid straight line passing through origin is a line of identity and dashed line is a smooth for observed versus predicted concentrations.

Figure S2. Conditional weighted residuals (CWRES) versus population predicted (PRED) LTG concentrations, by stage of pregnancy (PC, preconception; PP, postpartum). A solid line ($y = 0$) is included as a reference for CWRES. Dashed line is a smooth for CWRES versus PRED concentrations.

Figure S3. Conditional weighted residuals (CWRES) versus gestational age (GA). A solid line ($Y = 0$) is included as a reference for CWRES. Black dashed line is a smooth for CWRES versus GA.

Figure S4. Standardized visual predictive check (SVPC) plot of the final model. $P_{i,j}$, a percentile for the jth observation of the ith individual calculated from the marginal distribution of the model-simulated concentrations. Open circles, calculated $P_{i,j}$ values; dashed lines, 5th, 50th, and 95th percentiles (from bottom to top). Vertical bold dashed line at 40 weeks represents approximate time of delivery (0 weeks: preconception; 0–40 weeks: pregnant; >40 weeks: postpartum).

